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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,833	11/30/2001	Philip E. Thorpe	4001.002299	8102

23720 7590 09/08/2004

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EXAMINER

FETTEROLF, BRANDON J

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,833	THORPE ET AL.	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 03 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-10,23-27,41 and 49-68 is/are pending in the application.
- 4a) Of the above claim(s) 51-56, 60 and 66-67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4,6,7,27,49,50,63 and 68 is/are rejected.
- 7) ☒ Claim(s) 5,8-10,23-26,41,57,58,61,62,64 and 65 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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Thorpe *et al*

Date of Priority: 7/13/1998

DETAILED ACTION

Election/Restrictions

The Election filed on August 3, 2004 in response to the Office Action of July 7, 2004 is acknowledged and has been entered. Claims 4-10, 23-27, 41 and 49-68 are pending in the application

Applicant's election with traverse of Group I, claims 4-10, 23-27, 41, 49-50, 57-58, 61-65 and 68, as specifically drawn to a method of treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof and at least a second chemotherapeutic agent or a compound that interferes with tubulin activity has been acknowledged. The traversal is on the ground(s) that the requirement attempts to restrict claims that are in the same class and subclass; ignores proper generic and linking claims; omits reasoning, or offers inadequate reasoning, to support restriction; and fails to establish a burden on the examiner should the claims not be restricted. In addition, the requirement is also in contradiction with earlier decisions of the Office that the present claims are all drawn to the same patentable invention. These arguments have been considered and are not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in the restriction requirement of June 7, 2004.

In response to the applicant's argument that the requirement is a contradiction with earlier decisions of the Office with respect to the present claims all drawn to the same patentable invention the examiner answers as follows: In the parent application, 09/351, 543, now U.S. Patent 6,406,693 claim 4 is specifically drawn to a method of treating an animal having a vascularized tumor, comprising administering at least a first antibody that binds to an aminophospholipid of the vascular tumor, further comprising in claim 28 at least a second anti-cancer agent, wherein the second

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anticancer agent (claim 29) is a chemotherapeutic, radiotherapeutic, anti-angiogenic or apoptosis-inducing agent. In the present application, 09/998,833, the claims are specifically drawn to a method comprising administering a composition comprising at least a first antibody and a second therapeutic agent, wherein said second therapeutic agent is a chemotherapeutic agent, an anti-angiogenic agent, an inflammatory cytokine, H_2O_2 , thrombin, a compound that interferes with tubulin activity, or a calcium flux inducing agent, each of which are distinct their mechanism of action and also, chemical structure.

As to the question of burden of search, each "second" therapeutic agent is classified within a different subclass which would necessitate different searches of the US Patents and literature. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 4-10, 23-27, 41 and 49-68 are currently pending in the application.

Claims 51-56, 60 and 66-67 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 4-10, 23-27, 41, 49-50, 57-58, 61-65 and 68 are currently under consideration.

Species/Election

Applicant's election of a species without traverse of vincristine, Claims 50 or 58, in the reply filed on August 3, 2004 is acknowledged. However, upon review and reconsideration the species election is withdrawn.

Specification

The disclosure is objected to because of the following informalities: The specification, on numerous pages, refers to U.S. Applications incorporated herein by reference but does not contain the corresponding patent number. For example, the specification discloses:

Page 139, lines 8-11, U.S. Application Serial No. 08/295,868 (Patent No. 5, __, __), 08/350,212 (Patent No. 5, __, __), 08/482,369 (U.S. Patent 5, __, __), 08/457, 427 (U.S. Patent 5, __, __), and 08/479, 727 (U.S. Patent 5, __, __);

Page 139, lines 20-22, U.S. Application Serial Nos. 08/484, 369 (U.S. Patent 5, __, __), 08/487,427 (U.S. Patent 5, __, __), and 08/479, 727 (U.S. Patent 5, __, __);

Page 142, lines 15-16, U.S. Application Serial No. 08/295,868 (Patent No. 5, __, __);

Page 143, lines 5-7, U.S. Application Serial No 08/350, 212(U.S. Patent 5, __, __), 08/482,369 (U.S. Patent 5, __, __), 08/487,427 (U.S. Patent 5, __, __), and 08/479,727 (U.S. Patent 5, __, __);

Page 143, lines 24-25, U.S. Application Serial No 08/295, 868 (Patent No. 5, __, __), 08/350, 212 (Patent No. 5, __, __);

Page 144, line 20, Patent No. 5, __, __ (Application Serial No. 08/350,212); and

Page 146, Lines 17-20, U.S. Application Serial No. 08/472, 631 (U.S. Patent 5, __, __), 08/487,427 (U.S. Patent 5, __, __) and 08/481,904 (U.S. Patent 5, __, __).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 63 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 63 is rejected as vague and indefinite for reciting "biologically effective time" in claim 63. The term "biologically effective time" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 68 is rejected as vague and indefinite for reciting "second therapeutic agent" in claim 68. The term "second therapeutic agent" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 4, 27, 49 and 68 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4, 27-29, 42, 47 and 68 of U.S. Patent No. 6406693. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of both the instant claims and the patented claims overlap. In the instant case both set of claims are directed to a method of treating an animal having a vascularized tumor comprising simultaneously or sequentially administering a therapeutically effective

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combination of a least at least a first antibody or antigen-binding fragment thereof, that binds to an amino-phospholipid, and at least a second therapeutic agent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 4, 6-7, 49-50 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al (International Journal of Oncology, 10, 901-904, May, 1997) in further view of Tschmelitsch et al. (Cancer Research 57, 2181-2186, June 1, 1997).

In the instance case, Claim 4 is drawn to a method of treating an animal, comprising administering a therapeutically effective combination of at least a first monoclonal antibody or antigen binding fragment thereof that binds to an aminophospholipid and at least a second chemotherapeutic agent or a compound that interferes with tubulin activity.

Fishman *et al.* teaches the use of purified IgG anti- phosphatidylserine (*anti-PS*) antibodies as an effective treatment for melanoma (abstract). Fishman further teaches that the anti-PS antibodies exerted an inhibitory effect of 76% on the development of lung metastatic foci in mice inoculated with B-16 melanoma cells (page 903, 1st column, 2nd paragraph).

Fishman *et al.* does not teach administration of anti-phosphatidylserine (anti-PS) antibodies in combination with a chemotherapeutic.

Tschmelitsch *et al.* teaches (title) an enhanced antitumor activity of combination radio immunotherapy with chemotherapy (fluorouracil). For example, the reference teaches (page 2182, 2nd column, 2nd full paragraph) that in an earlier study, mAb A33 alone showed no demonstrable effect on growth of established tumors, but that the combination of 5FU (*fluorouracil*) and ¹³¹I-mAb A33 resulted in significantly higher antitumor activity (figure 4).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine a chemotherapeutic agent with antibodies. As evidenced by

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Tschmelitsch *et al*, it is well known in the art that chemotherapeutics, such as fluoruracil, when used in combination with specific antineoplastic antibodies, can enhance the anticancer effects versus the effects when either agent is used alone. Thus, one of ordinary skill in the art would have a reasonable expectation that by combining chemotherapy with the anti-phosphatidylserine antibodies used by Fishman *et al*, one would achieve enhanced antineoplastic effects.

Claims 5, 8-10, 23-26, 41, 57-58, 61-62, and 64-65 are objected to for being dependent from a rejected base claim.

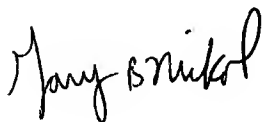
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

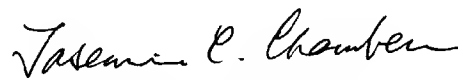
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF



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PRIMARY EXAMINER**



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